

Title: Cytokine storm in COVID-19 and parthenolide: preclinical evidence

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Abstract

A group of patients with pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported from China in December 2019. Although several antiviral drugs are widely tested, none of them has been approved as specific antiviral therapy for coronavirus disease 2019 (COVID-19). Accumulating evidence established a hyperinflammatory states or cytokine storm in COVID-19. Among these cytokines, IL-6 plays a key role in cytokine storm and can predict the adverse clinical outcomes and fatality in these patients.

Based on the evidence of the significant role of IL-6 in cytokine storm, diabetes mellitus and cardiovascular diseases as principal comorbidities, it seems that anti-cytokine therapy may be useful in patients with severe COVID-19 to reduce mortality. Recent studies demonstrated that herbal-derived natural products had immunosuppressive and anti-inflammatory properties and exhibited exceptional act on mediators of inflammation. Parthenolide is the principal sesquiterpene lactones and the main biologically active constituent *Tanacetum parthenium* (commonly known as feverfew) which has could significantly reduce IL-1, IL-2, IL-6, IL-8, and TNF- α production pathways established in several human cell line models in vitro and in vivo studies. Therefore, parthenolide may be one of the herbal candidates for clinical evaluation.

Key words: Coronavirus; Parthenolide; COVID-19; *Tanacetum parthenium*; Feverfew

Dear Editor,

A group of patients with pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported from China in December 2019 (Tu et al. 2020; Clerkin et al., 2020; Guo et al., 2020). It rapidly spread throughout the world and led to a fatal pandemic (Clerkin et al., 2020; Cao, 2020). Up to now, although several antiviral drugs are widely tested, none of them has been approved as specific antiviral therapy for coronavirus disease 2019 (COVID-19), and the mainstay of treatment is based on the management of patient's symptoms (Tu et al. 2020; Cao, 2020). Therefore, vaccines, monoclonal antibodies (mAbs), and novel therapies are of interest worldwide (Tu et al. 2020; Clerkin et al., 2020; Cao, 2020). Accumulating evidence established a hyperinflammatory states or cytokine storm in COVID-19. Elevated levels of inflammatory cytokines, including interleukin-2 (IL-2), IL-6, IL-8, IL-17, IL-1 β , and tumor necrosis factor-alpha (TNF- α), which damage the heart, liver, and kidneys may play a significant role in the pathogenesis of COVID-19, leading to shock as well as respiratory and multiorgan failure (Guo et al., 2020; Cao, 2020; Zhang et al., 2020). Among these cytokines, IL-6 plays a key role in cytokine storm and can predict the adverse clinical outcomes and fatality in these patients (Tu et al., 2020; Guo et al., 2020; Zhang et al., 2020). Interleukin-6 is a two-faced cytokine and considered a pro-inflammatory and anti-inflammatory cytokine, which is produced by immune cells. Its serum levels in the healthy state prepare immune responses of the host and sustained overproduction of IL-6 is involved in a number of inflammatory diseases (Tue et al., 2020; Cao, 2020; Zhang et al., 2020). A high level of IL-6, which is detected in patients with severe and complicated COVID-19, has a relationship with decreased lung elasticity and more severe bronchoalveolar inflammation. Furthermore, elevated levels of circulating IL-6 significantly correlated with the need for mechanical ventilation and poor outcome in patients with severe COVID-19 which were complicated by pneumonia and acute respiratory distress syndrome (ARDS) (Tue et al., 2020; Cao, 2020; Zhang et al., 2020). Interleukin-6 participates in the pathogenesis of common comorbidities of COVID-19 e.g., diabetes mellitus (DM) and cardiovascular diseases (CVDs) (Gue et al., 2020; Zhang et al., 2020). In addition, considerably elevated levels of circulating IL-6 were seen in COVID-19 patients with DM and myocardial injury. The data supports the fact that DM is a risk factor for rapid deterioration and poor prognosis of COVID-19 (Clerkin et al., 2020; Guo et al., 2020).

Based on the evidence of the significant role of IL-6 in cytokine storm, DM, and CVDs, it seems that anti-cytokine therapy such as Tocilizumab (Anti-IL-6R) may be useful in patients with severe COVID-19 to reduce mortality (Tu et al., 2020; Clerkin et al., 2020; Zhang et al., 2020). The use of Tocilizumab in a preliminary investigation has quickly reduced fever and improved respiratory function in these patients and there are ongoing clinical trials (Tu et al., 2020; Clerkin et al., 2020; Cao, 2020). Recent studies demonstrated that herbal-derived natural products had immunosuppressive and anti-inflammatory properties and exhibited exceptional act on mediators of inflammation. *Curcuma Longa*, *Glycyrrhiza Species*, *Camellia Sinensis*, *Salvia Miltiorrhiza* and *Tanacetum parthenium*, have indicated immunomodulatory properties by reducing pro-inflammatory cytokines and mediators (Amirghofran, 2012). *Tanacetum parthenium* (commonly known as feverfew) prevents releasing of pro-inflammatory mediators from macrophages and lymphocytes (Amirghofran, 2012; George et al., 2012). This is a perennial plant, frequently grows in various regions of the world. The history of medical application of feverfew backs to ancient Greek, Dioscorides prescribed this plant for reducing fever and “all hot inflammations”. Therefore, it was called the “medieval aspirin” (Pareek et al., 2011). Feverfew has been used in traditional and folk medicine for the treatment of fever, cold, asthma, migraine headache, arthritis, women's health issues, inflammatory conditions, etc. (George et al., 2012; Pareek et al., 2011). Although the qualitative standard of many trials in the phytopharmacological field are less rigorous than the conventional pharmaceutical sector (Williamson et al., 2020), clinical evidence suggests that feverfew extract might have positive results in migraine prevention (Lopresti et al., 2020). Phytochemical studies have shown the presence of many active ingredients of feverfew, including sesquiterpene lactones, flavonoid glycosides, sesquiterpenes, and monoterpenes. Parthenolide is the principal sesquiterpene lactones and the main biologically active constituent in this plant (Pareek et al., 2011), which has different pharmacological properties, including antioxidant, anti-inflammatory, analgesic, antimicrobial, anti-migraine, and anticancer activities (George et al., 2012; Wang et al., 2015). Moreover, parthenolide has been shown potent inhibitory effects on pro-inflammatory pathways such as NF- κ B and LPS pathways. Interestingly, parthenolide could significantly reduce IL-1, IL-2, IL-6, IL-8, and TNF- α production pathways established in several human cell line models *in vitro* (monocytes, macrophages, neutrophils) and *in vivo* studies (Wang et al., 2015; Magni et al., 2012). Although specific blockade of pro-inflammatory cytokines using mAbs is one of the main therapeutic

strategies for the management of cytokine storm in COVID19, parthenolide may be one of the herbal candidates for clinical evaluation.

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References

- Amirghofran Z. (2012). Herbal medicines for immunosuppression. *Iran J Allergy Asthma Immunol*, 11:111-9.
- Cao X. (2020). COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*, 20:269-270.
- Clerkin KJ, Fried JA, Raikhelkar J, et al. (2020). Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation*, 2020. Mar 21
- George V, Kumar D, Suresh P, Kumar R. (2012). A review on the therapeutic potentials of parthenolide: a sesquiterpene lactone. *Int Res J Pharmacy*, 3(2):69-73
- Guo W, Li M, Dong Y, Zhou H, et al. (2020). Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*, 2020 Mar 31:e3319
- Lopresti AL, Smith SJ, Drummond PD. (2020). Herbal treatments for migraine: A systematic review of randomised-controlled studies. *Phytother Res*, 2020;10.1002/ptr.6701
- Magni P, Ruscica M, Dozio E, Rizzi E, Beretta G, Facino RM. (2012). Parthenolide Inhibits the LPS-induced Secretion of IL-6 and TNF- α and NF- κ B Nuclear Translocation in BV-2 Microglia. *Phytother Res*, 26:1405-9
- Pareek A, Suthar M, Rathore GS, Bansal V. (2011). Feverfew (*Tanacetum parthenium* L.): A systematic review. *Pharmacogn Rev*, 5: 103–110
- Tu YF, Chien CS, Yarmishyn AA, et al. (2020). A Review of SARS-CoV-2 and the Ongoing Clinical Trials. *Int J Mol Sci*, 21(7):2657
- Wang M, Li Q. (2015). Parthenolide could become a promising and stable drug with anti-inflammatory effects. *Nat Prod Res*, 29:1092-101
- Williamson EM, Liu X, Izzo AA. (2020). Trends in use, pharmacology, and clinical applications of emerging herbal nutraceuticals. *Br J Pharmacol*, 177(6):1227-1240
- Zhang C, Wu Z, Li J-W, et al. (2020). The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents*, 2020 Mar 29:105954.